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Modified Atkins diet to children and adolescents with medical intractable epilepsy

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ABSTRACT

The aim of the present study was to evaluate the tolerability and efficacy of the modified Atkins diet given to children and adolescents with antiepileptic drug (AED) treatment resistant epilepsy.

15 children with medically intractable epilepsy were enrolled in the study. Inclusion criteria were at least one seizure a week and a trial of at least two AEDs without obtaining seizure freedom documented in a seizure calendar.

At baseline subjects initiated a diet with carbohydrates restricted to make up 10 energy percent. If seizures were reduced by less than 50% after 7–14 days carbohydrates were further restricted to 10 g per day. No change in AED treatment was allowed.

The diet was well tolerated. After 3 months six out of the fifteen children (40%) had a seizure reduction of more than 50%, which was seen in different epileptic syndromes and different age groups. The responders reported an increase in quality of life and cognition. At 12 months follow-up 3 (20%) continued the diet with an unchanged marked seizure reduction.

The present study confirms the high tolerability and effect of the modified Atkins diet on seizure control in AED treatment resistant epilepsy. Further larger prospective studies are however needed to confirm these results.

Introduction

The ketogenic diet was originally developed in USA in the early 1920s. After the appearance of effective treatment with antiepileptic drugs like phenytoin and carbamazepine, the diet was more or less forgotten until the late 1990s, when it was reintroduced. Treatment with the diet has since then become increasingly accepted internationally and it is today considered an important alternative to antiepileptic drug therapy in young children with medically intractable seizures.[1] The ketogenic diet is however difficult to introduce to older children and adolescents[2] and requires the parents to be highly motivated in order to successfully maintain this very restricted diet. One study showed that less than 10% continued the diet at 12 months follow-up probably because of loss of compliance.[3]

The modified Atkins diet is a less restrictive alternative to the traditional ketogenic diet, which allows an unlimited protein and fat intake and does not restrict calorie or fluid intake.

Recent studies of the modified Atkins diet at two different centers have shown that it is an effective and well-tolerated treatment in children.[4–7]

The aim of the present study was to evaluate the immediate tolerability and efficacy of treatment with a modified Atkins diet given in a European country for 3 months to medically intractable children and adolescents with epilepsy. Further, a 12-month follow-up evaluation has been added to the study.

Methods

Subjects

15 children (6 female, 9 male) aged 2–17 years at diet onset (median 10 years) with medically intractable childhood epilepsy were enrolled from November 2006 until February 2007. Three of the children were on a waiting list for the classical ketogenic diet at the time of enrolment. Of the remaining children none of their parents had specifically asked for treatment with the ketogenic diet or the Atkins diet. They were all enrolled in the study via an ordinary outpatient clinic.

Including criteria were a minimum of one weekly seizure of any type, a trial of at least two relevant antiepileptic drugs (AED)

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without obtaining seizure freedom documented by a seizure calendar. In children with many daily seizures an estimated number was calculated from counting seizures for 1 or 2 h at a specific time every day. A variety of epilepsy syndromes were included.

10 patients were treated at Dianalund Epilepsy Center, 4 at Rigshopitalet and 1 at Hvidovre Hospital. Oral and written informed consent was obtained from all families prior to initiation of the study, which was approved by the Ethical Committee of Copenhagen and Frederiksberg Municipalities ((KF) 01 320592).

Diet principles

In the out patient clinic parents were instructed to use a formula to calculate the content of carbohydrates from labels on food products. This formula helped parents control the daily carbohydrate content of their children's diet, so that dietician counselling was not needed on a daily basis.

Carbohydrates were restricted to make up 10 energy percent and restricted further to 10 g per day after 7–14 days, if seizures were not reduced by >50% by then. Patients were further encouraged to use fibre supplements and to choose fibrous carbohydrates as fruit and vegetables to avoid constipation as a side effect. No restrictions were given with regard to energy, fluids, proteins and fats intake, however intake of fats were encouraged. If marginal efficacy was observed an increased intake of lipids was encouraged.

4 daily meals each containing 25% of the daily carbohydrate contents were recommended. No restrictions were given on carbohydrate free meals. Intake of low-carbohydrate products (e.g. candy bars, baking mixes) was discouraged for at least the first month. Especially carbohydrate-free soft drinks, pork crackling and carbohydrate-free jelly were suggested as alternatives to sweets. Further, vitamin and mineral supplementation was recommended.

The same dietician (SW) was responsible for all contacts with the families throughout the study period. An estimation of time spent by the dietician and the medical doctors showed that an average of 45 min at the first visit and 30 min at each of the following visits was used. In addition approximately 6 h were spent on each family for telephone and email correspondences.

Upon completion of the study parents were invited to continue the diet supported by their regular dietician, if the child had experienced a reduction in seizures including children with less than 50% seizure reduction. Adjustment in AED treatment was allowed and contact to dietician and out patient clinics was reduced to once every third month.

Design

All patients were evaluated at baseline and every month for 3 months in total. Blood tests included liver enzymes, cholesterol and triglyceride. Before entering the study plasma carnitine and urine were analysed to exclude any neurometabolic disorder. The diet was regularly followed up by the dietician via e-mail or telephone. No change in AED treatment was allowed. Parents were asked to measure urinary ketones on a daily basis for the first month of the study and weekly from the second month and throughout the study (Table 1).

Parents were instructed to use a visual analogue scale (VAS) to assess cognition, quality of life and appetite of their children as well as their own motivation at the beginning and 3 months after initiation of the diet.

VAS scores were converted into percentage, the highest percentage being a positive statement and the lowest percent being a negative.

A follow-up was performed at 12 months. The follow-up comprised a case note search and a clinical visit for the children still treated with the diet.

Statistics

Means were compared using a two sample paired Students *t*-test, and level of significance was set at $p \leq 0.05$. Tests were performed using Excel Office for Mac 2004.

Results

Three children (20%) did not complete the study. Two were excluded within the first month of the study because of change in AED treatment (no effect on seizures and intolerable high seizure frequency). One of these patients changed to the ketogenic diet without efficacy. The third patient stopped after 2 months because of no efficacy of the diet. Two patients (13%) stopped because of side effects after completion of the 3 months trial.

Six of the 15 (40%) were responders with a seizure reduction of more than 50% after 3 months. Seizure reduction was seen in a variety of different epileptic syndromes as well as different age groups (Table 2).

At 10 energy percent 14 children (93%) measured ketones. One patient excluded early in the study did not measure ketones. Moderate urinary ketosis appeared in 12 (86%) of the 14 children within 10 days (mean 2.9 days). Two children (14%) developed only mild ketosis.

At 10 g carbohydrate 13 children (87%) measured ketones. Mild to moderate ketosis continued. Only few times strong ketosis appeared and never for a longer period. Parents reported no correlation between degree of ketosis and seizure reduction.

All except one child reduced their daily carbohydrate intake from 10 energy percent to 10 g. This child (no. 12) had a >50% reduction in seizures despite the high carbohydrate intake of 10 energy percent (32 g per day). Patients who were non-responders and increased lipid intake did not improve seizure control.

Four patients reported side effects of the treatment but all of them completed the study. Three felt constipated and one complained of nausea.

Table 1
Study design.

Baseline	1-month	2-month	3-month
Diet information	Diet adjustments	Diet adjustments	Diet adjustments
Diet instruction	Seizure registration	Seizure registration	Seizure registration
Registration of last months number of seizures	Grade of ketosis	Grade of ketosis	Grade of ketosis
Blood test	Blood tests	Blood tests	Blood tests
Weight	Weight	Weight	Weight
Diet initiation when blood tests were cleared			Parents motivation, the child's appetite QOL and cognition
Parents motivation, the child's appetite			3 days weighed dietary calendar
QOL and cognition			

Table 2
Patient characteristics and outcome of a 3 months trial with a modified Atkins diet.

Patient	Syndrome	Mental retardation	Age	Monthly seizure number before	Monthly seizure number after	% reduction
1	LG	+	6	30	–	–
2	MAE	+	14	37	38	0
3	SF	+	9	10	10	0
4[a]	CAE	–	11	210	30	>85
5[a]	MAE	+	3	300	10	>90
6	SF	–	2	600	–	–
7	SF	–	12	600	450	25
8[a]	SF	+	12	44	21	>50
9	SF	+	15	25	21	0
10	LG	+	11	180	180	0
11	LG	+	5	25	–	–
12[a]	MAE	+	15	540	30	>90
13[a]	SF	+	10	150	60	>50
14[a]	JME	–	17	150	30	>75
15	SF	–	13	60	60	0

SF, symptomatic focal; LG, Lennox Gastaut; MAE, myoclonic astatic epilepsy; CAE, childhood absence epilepsy; JME, juvenile myoclonic epilepsy.
[a] Responders.

Cholesterol increased from 4.0 mmol/l (S.D. ± 0.9) to 5.3 mmol/l (S.D. ± 1.5) ($p = 0.02$). Triglycerides were 1.03 mmol/l (S.D. ± 0.41) at baseline and 1.29 mmol/l (S.D. ± 0.75) ($p = 0.28$) after 3 months.

The weight increased with a mean of 0.7 kg during the study period. The mean weight was 41.8 kg at baseline and 42.8 kg after 3 months ($p = 0.41$). Eight children lost weight with a median of 0.5 kg (range, 0.1–6.5 kg) and five gained weight with a median of 2.35 kg (range, 0.1–4.1 kg). Two of those who lost weight were overweight at start of the study.

11 parents assessed the cognition of their children, quality of life and appetite at baseline and after 3 months by VAS (Tables 3 and 4). 10 parents assessed their own motivation in relation to beginning the diet, also by VAS. Responders increased their cognition and quality of life, while their motivation and appetite was unchanged. In non-responders motivation and appetite decreased while quality of life and cognition in general were unchanged throughout the study period.

All children with less than 50% seizure reduction stopped the diet after 3 months. At the 12 months follow-up three patients (patient no. 5, no. 12, no. 14) had continued the diet with the same or even an increased seizure reduction compared to the 3 months follow-up. One of these patients (no. 14) had tapered her antiepileptic drug. The remaining three responders stopped the diet after 5–8 months as parents and the children felt that the obtained seizure reduction was not enough to motivate a continuation.

Discussion

This study has shown that 12 of 15 children continued a modified Atkins diet for 3 months in a population of rather old children (mean age 10) and in a setting with few supportive resources when compared to the classical ketogenic diet. Except for three children enrolled from the ketogenic diet waiting list, parents had no special motivation for diet intervention but complied well. This indicates that the diet is tolerable and thus might become a more widely used alternative treatment compared to the classical ketogenic diet. Similar studies have reported a frequency of 80% and 64% of subjects continuing their diets at 3 months follow-up.[6,7]

Using an intent to treat analysis six of 15 children (40%) had more than 50% seizure reduction after 3 months. This is rather similar to the above-mentioned studies. Kossoff et al.[6] showed that children starting the diet at 10 g carbohydrate per day had a significantly higher likelihood of more than 50% seizure reduction when compared to children starting at 20 g carbohydrate per day. The authors therefore suggested the opposite strategy as in our study. Comparing the results at 3 months follow-up at John Hopkins Hospital resulted in comparable figures between the modified Atkins diet and the classical ketogenic diet.[5] Larger and more studies are however needed in order to clarify a possible difference in treatment effect between the two diets.

The present study is the first to provide a 12 months follow-up with 3 out of 15 (20%) patients continuing the diet. The maintained efficacy of the diet treatment must be seen in the light of the patient population consisting of children who are difficult to treat.

It is not easy to find comparable add-on studies on the efficacy of introducing a new antiepileptic drug in children with ongoing seizures despite treatment. Two studies with a follow-up of 12 months found that 40% (vigabatrin) and 31% (levetiracetam) had >50% seizure reduction.[8,9] One study gave results at 18 months follow-up and had 32% with >50% seizure reduction (zonisamide) while a study with 24 months follow-up found that 23% (topiramate) had >50% seizure reduction.[10,11] It is difficult to compare the severity of the epilepsy of the children involved, however.

Table 3
Quality of life (QOL), cognition, motivation and appetite measured by visual analogue scale (VAS) at baseline and at 3 months follow-up in responders to the diet.

Responders (6 patients)	Baseline (%)	Follow-up (%)
QOL	43	68
Cognition	53	68
Motivation	97	94
Appetite	66	67

Data are presented in mean percent.

Table 4
Quality of life (QOL), cognition, motivation and appetite measured by visual analogue scale (VAS) at baseline and at 3 months follow-up in non-responders to the diet.

Non-responders (5 patients)	Baseline (%)	Follow-up (%)
QOL	49	39
Cognition	49	50
Motivation	94	52
Appetite	54	42

Data are presented in mean percent.

Our study population included a 17-year-old girl (no. 14) who continued the diet at 12 months follow-up. She managed the diet herself, went on holiday and cafés with her friends and even tapered Lamictal treatment without loosing control of her seizures.

The first trial of the modified Atkins diet for 30 adults revealed that 33% had more than 50% seizure reduction after 6 months of treatment.[12] A smaller European study on adults also concluded that the diet is feasible in adults.[13]

As expected the quality of life, cognition, motivation and appetite were rated high at 3 months follow-up among responders compared to non-responders. One study have found that quality of life might improve even with seizure reduction less than 50% in the classical ketogenic diet.[14]

Since the Atkins diet originally was created in order to loose weight it is reassuring that the mean weight of the children was the same at baseline and at the 3 months follow-up. We found a significant increase in cholesterol which was however small, while triglycerides were unchanged. These findings are in accordance with another study testing the Atkins diet.[6]

Few children and parents had specific complaints concerning the diet. At the 3 months follow-up it was however obvious that only those with a substantial seizure reduction chose to continue the diet.

Levels of ketones increased somewhat when the intake of carbohydrate decreased, but though ketones are widely used as markers of seizure control, our findings support that a high ketosis per se is not always essential for an improvement in seizure control.

This small study confirms the positive effect of the modified Atkins diet on seizure control in AED treatment resistant epilepsy and further provides encouraging results regarding seizure control at the 12 months follow-up. Larger prospective studies are needed to confirm these results including a comparison between the ketogenic diet and the modified Atkins diet.

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